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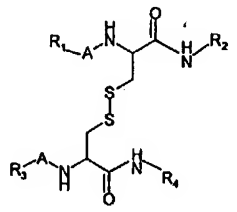

(I)

(57) Abstract

Subject of the present invention are pharmaceutical compositions containing nonpeptidic cystine derivatives of general formula (I) wherein R_1 and R_3 may be the same or different and are selected from hydrogen, an aromatic or non–aromatic carbocyclic or heterocyclic ring or a linear or branched saturated or unsaturated alkyl group of 1 to 15 carbon atoms which can be interrupted by a hetero atom and which can be substituted by an aromatic or non–aromatic carbocyclic or heterocyclic ring. R_2 and R_4 may be the same or different and are selected from hydrogen, a linear or branched, saturated or unsaturated alkyl group of 1 to 15 carbon atoms which can be interrupted by a hetero atom and which can be substituted by an aromatic or non–aromatic carbocyclic or heterocyclic ring and A is a valency bond or a –CO–, $–SO_2–$, –NHCO–, –NHCS– or –O–CO– group, their pharmacologically acceptable salts and optically active forms thereof and pharmaceutically acceptable carriers, for the treatment of diseases selected from tumor growth and metastasis, inflammatory diseases like osteo– and rheumatoid arthritis, osteoporosis, multiple sclerosis, periodontitis, restenosis, diseases caused by bacteria such as meningitis, sun–induced skin aging and Alzheimers disease and new compounds.

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CYSTINE DERIVATIVES AS THERAPEUTIC AGENTS FOR MATRIX METALLOPROTEASE RELATED DISEASES

The invention relates to the use of compounds of formula I as pharmaceuticals and the use of such pharmaceuticals as drugs to treat diseases such as tumor growth and metastasis, inflammatory diseases like osteo- and rheumatoid arthritis, osteoporosis, multiple sclerosis, periodontitis, restenosis, diseases caused by bacteria such as meningitis, sun-induced skin aging and Alzheimers disease.

The family of matrix metalloproteases (MMPs) has become a major target for drug design, since these enzymes are involved in tissue remodeling and connective tissue turnover, and thus in several diseases where (i) rapid extracellular matrix degradation is taking place, e.g. during congestive heart failure and extravasion of highly metastatic tumor cells, or (ii) slow extracellular matrix degradation is occurring, e.g. artherosclerotic lesion formation and rupture, cartilage matrix loss in osteoarthritis, bone matrix degradation in osteoporosis, gingival degradation in periodontal disease, matrix remodeling and deposition in Alzheimer plaque formation and rheumatoid arthritis.

The MMP family currently includes seventeen members, thirteen of which are secreted from the cells in a soluble form and four members are membrane-bound enzymes. The MMPs are zinc dependent and calcium requiring enzymes which are inhibited by one of the members of the tissue inhibitor of metalloproteinase (TIMP) family. Synthetic inhibitors of this class of enzymes have been developed as hydroxamates, N-carboxyalkyl derivatives, phosphonamidates and phosphinates as well as by using thiol groups as ligands for the active-site zinc atom.

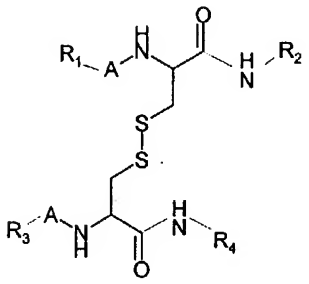
3D-structures of the complexes between the catalytic domains of MMPs and various inhibitors have been published as well as the structure of the proenzyme of MMP-3 with an N-terminal propeptide of about 80 residues. The propeptide forms a separate smaller domain that contains three α-helices and an extended peptide that occupies the active site. The catalytic domain in all these structures contains two Zn^{2+} ions, i.e. a "structural" zinc ion and a "catalytic" zinc ion. The "catalytic" zink ion is coordinated by the side chains of three histidyl residues of the consensus sequence HEXXHXXGXXH. The fourth ligand of the "catalytic" zink in the inhibited enzymes is a coordinating group of the inhibitors like the hydroxamate or carboxylate; in the pro-MMP propeptide it is the thiol group of the cysteine residue.

Correspondingly, the thiol-based collagenase inhibitors, proposed so far, are generally of peptidic structure containing cysteine or cysteine-like amino acids and their design was based on the binding mode of the substrate and more recently, of the cysteine-containing propeptide.

Recently Müller et al. (Biol. Chem 378, 1475-1480 (1997)) described a new class of MMP inhibitors which were derived from cysteine in a non-peptidic manner.
Some cysteine derivatives are disclosed therein as intermediates to prepare the final cystin derivatives but no pharmaceutical use of these cystine derivatives is disclosed or predicted.

Surprisingly we now have found that similar disulfide compounds, i.e. cystine derivatives are highly active in vivo. In fact these inhibitors are not active against matrix metalloproteases (i. e. Ki > 10μM). However, activity can be demonstrated in matrix metalloprotease related diseases like tumor growth and metastasis. Indeed these compounds are better than the inhibitors cited in the paper of Müller et al.

Subject of the present invention are nonpeptidic cystine derivatives of the general formula I



(I)

wherein

R_1 and R_3 may be the same or different and are selected from hydrogen, an aromatic or non-aromatic carbocyclic or heterocyclic ring or a linear or branched saturated or unsaturated alkyl group of 1 to 15 carbon atoms which can be interrupted by a hetero atom and which can be substituted by an aromatic or non-aromatic carbocyclic or heterocyclic ring.

R_2 and R_4 may be the same or different and are selected from hydrogen, a linear or branched, saturated or unsaturated alkyl group of 1 to 15 carbon atoms which can be interrupted by a hetero atom and which can be substituted by an aromatic or non-aromatic carbocyclic or heterocyclic ring and

A is a valency bond or a-CO-, -SO_2-, -NHCO-, -NHCS- or –O-CO-group

their pharmacologically acceptable salts and optically active forms thereof and pharmaceutically acceptable carriers.

With respect to formula I R_1 or/and R_y represent a branched saturated or unsaturated alkyl group of 1 to 15 carbon atoms selected from methyl, ethyl, propyl, n-butyl, tert-

butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, etc., vinyl, etc. as well as the corresponding alkinyl groups e. g. acetylene.

The carbocyclic aromatic or non aromatic alone or as substituents for said alkyl groups are selected from C_3-C_6 cycloalkyls such as cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl, or C_6-C_{14} carbocyclic aromatic substituents such as phenyl, naphthyl, fluorenyl, fluorenonyl or anthranyl, or heterocyclic non aromatic substituents such as pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl, or heterocyclic aromatic substituents such as pyrrolyl, pyridinyl, furyl, thienyl, thiazolyl, imidazolyl, pyrimidinyl, purinyl, indolyl, quinolyl, carbazolyl.

The carbocyclic aromatic or non aromatic ring systems respectively heterocycles can optionally be substituted once or several times for example by halogen-, nitro-, hydroxy-, C_1-C_6 alkyl-, C_1-C_6 alkoxy-, amino-, mercapto-, carboxyl-, cyano-, benzoyl, phenoxy or methylsulfonyl groups.

The alkyl group can be interrupted by a heteroatom, preferably by O, N, S.

A preferably denotes the group –CO-, -SO_2- and –O-CO-.

If A denotes –CO-, the groups R_1 and R_3 are preferably selected from the following residues:

hydrogen, C_1-C_6-alkyl, fluorenyl, fluorenonyl, phenyl, benzyl or styryl whereby the phenyl rings may be substituted by chloro, methyl, ethyl, methoxy, phenoxy, benzoyl or methylsulfonyl.

If A denotes -SO_2-, R_1 and R_3 are preferably selected from the following residues:

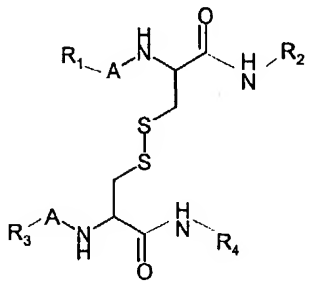
methyl, ethyl, toluolyl or phenyl.

If A denotes –O-CO-, R_1 and R_3 are preferably selected from the following residues: benzyl or phenyl optionally substituted by halogen.

R_2 and R_4 are preferably selected from the following residues:

phenethyl, phenylmethyl, phenylcyclopropyl, morpholinoethyl, morpholinopropyl, cyclohexylethyl, pyridylethyl, imidazolylethyl, indolylethyl or 4-chlorophenylethyl whereby the phenyl moities can be substituted by halogen, methyl or methoxy groups.

Subject of the invention are also new compounds of formula I



(I)

wherein

R_1 and R_3 may be the same or different and are selected from hydrogen, an aromatic or non-aromatic carbocyclic or heterocyclic ring or a linear or branched saturated or unsaturated alkyl group of 1 to 15 carbon atoms which can be interrupted by a hetero atom and which can be substituted by an aromatic or non-aromatic carbocyclic or heterocyclic ring.

R_2 and R_4 may be the same or different and are selected from hydrogen, a linear or branched, saturated or unsaturated alkyl group of 1 to 15 carbon atoms which can be interrupted by a hetero atom and which can be substituted by an aromatic or non-aromatic carbocyclic or heterocyclic ring and

A is a valency bond or a-CO-, -SO_2-, -NHCO-, -NHCS- or –O-CO-group

with the proviso that if R_2 and R_4 are benzyl, R_1-A and R_3-A cannot be formyl, C_1-C_{10} alkylcarbonyl, benzoyl, toluenesulfonyl or benzyloxycarbonyl, and

if R_1-A and R_3-A are benzyloxycarbonyl, R_2 and R_4 cannot be pyridylmethyl, phenylethyl, 4-hydroxyphenylethyl, 4-chlorophenylethyl, phenylpropyl or indolylethyl

their pharmacologically acceptable salts and optically active forms thereof.

The compounds of formula I can be prepared using classical methods of peptide chemistry.

Acylation of cystine or its carboxy protected derivatives with activated carboxylic or sulfonic acids like acid chlorides, active esters like N-hydroxysuccinimid or hydroxy benzotriazol esters. These activated esters may be prepared in situ using activating agents like carbodiimides or N,N'-carbonyldiimidazole followed by amidation of the carboxy group of the cystine using the methods of peptide chemistry.
Another method of preparation starts with carboxy protected cystine and reacting it with activated acids, isocyanates, isothiocyanates. After the cleavage of the protecting group the carboxylic function can be amidated as described above. Useful protecting groups are known from peptide chemistry e.g. methyl, ethyl, benzyl or p-tert.butylesters. Alkyl esters are cleaved by alkaline hydrolysis, benzyl esters by HBr in acetic acid. Tert.butyl esters are cleaved with strong organic acids like trifluoro acetic acid.

The compounds of the present invention are pharmacologically useful in the treatment of rheumatoid arthritis and related diseases in which collagenolytic activity is a contributing factor, such as, for example, corneal ulceration, osteoporosis, periodontitis, Paget's disease, gingivitis, tumor invasion, dystrophic epidermolysis, bullosa, systemic

ulceration, epidermal ulceration, gastric ulceration, and the like. These compounds are particularly useful in the treatment of rheumatoid arthritis (primary chronic polyarthritis, PCP), systemic lupus erythematosus (SLE), juvenile rheumatoid arthritis, Sjögren's syndrome (RA + sicca syndrome), polyarteritis nodosa and related vasculities, e. g. Wegener's granulomatosis, giant-cell arteritis, Goodpasture's syndrome, hypersensitiveness angiitis, polymyositis and dermatomyositis, progressive system sclerosis, M. Bechterew, Reiter syndrome (arthritis + urethritis + conjunctivitis), mixed connective tissue disease (Sharp's syndrome), spondylitis ankylopoetica (M. Bechterew).

The compounds of the present invention may be administered by any suitable route, preferably in the form of a pharmaceutical composition adapted to such a route and in dose effective for the treatment intended. Therapeutically effective doses of the compounds of the present invention required to prevent or arrest the progress of the medical condition are readily ascertained by one of ordinary skill in the art.

Accordingly, the invention provides a class of novel pharmaceutical compositions comprising one or more compounds of the present invention, in association with one or more non-toxic pharmaceutically acceptable carriers and/or adjuvants (collectively referred to herein as "carrier materials") and, if desired, other active ingredients. the compounds and compositions may, for example, be administered intravascularly, intraperitoneally, subcutaneously, intramuscularly or topically.

For all administrations, the pharmaceutical composition may be in the form of, for example, a tablet, capsule, suspension or liquid. The pharmaceutical composition is preferably made in the form of a dosage unit contained in a particular amount of the active ingredient. Examples of such dosage units are tablets or capsules. A suitable daily dose for a mammal may vary widely depending on the condition of the patient and other factors. However, a dose from about 0.1 to 300 mg/kg body weight, particularly from

about 1 to 30 mg/kg body weight may be appropriate. The active ingredient may also be administered by injection.

The dose regimen for treating a disease condition with the compounds and/or compositions of this invention is selected in accordance with a variety of factors, including the type, age, weight, sex and medical conditions of the patient. Severity of the infection and the role of administration and the particular compound employed and thus may vary widely.

For therapeutic purposes, the compounds of the invention are ordinarily combined with one ore more adjuvants appropriate to the indicated route of administation. If per os, the compounds may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanoic acids, cellulose alkyl ester, talc, stearic acid, magnesium stearat, magnesium oxide, sodium and calcium salts of phosphoric and sulphuric acids, gelatine, acacia, sodium alginate, polyvinyl-pyrrolidone and/or polyvinyl alcohol, and thus tabletted or encapsulated for convenient administration. Alternatively, the compounds may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cotton seed oil, peanut oil, sesam oil, benzyl alcohol, sodium chloride and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art. Appropriate dosages in any given instance, of course, depend upon the nature and severity of the condition treated, the route of administration and the species of mammal involved, including its size and any individual idiosyncracies.

Representative carriers, dilutions and adjuvants include, for example, water, lactose, gelatine starch, magnesium stearate, talc, vegetable oils, gums, polyalkylene glycols, petroleum gelly, etc. The pharmaceutical compositions may be made up in a solid form, such as granules, powders or suppositories, or in liquid form, such as solutions, suspensions or emulsions. The pharmaceutical compositions may be subjected to conventional pharmaceutical adjuvants, such as preservatives, stabilizers, wetting agents, emulsifiers, buffers, etc.

For use in the treatment of rheumatoid arthritis, the compounds of this invention can be administered by any convenient route, preferably in the form of a pharmaceutical composition adapted to such route and in a dose effective for the intended treatment. In the treatment of arthritis, administration may be conveniently be by the oral route or by injection intra-articularly into the affected joint.

As indicated, the dose administered and the treatment regimen will be dependent, for example, on the disease, the severity thereof, on the patient being treated and his response to treatment and, therefore, may be widely varied.

The following compounds are synthezised in analogy to Müller et al. (Biol. Chem. 378, 1475-1480 (1997)).They are new and subject of the invention:

1) 2-Formylamino-3-(2-formylamino-2-phenethylcarbamoyl-ethyldisulfanyl)-*N*-phenethyl-propionamide

2) 2-Acetylamino-3-(2-acetylamino-2-phenethylcarbamoyl-ethyldisulfanyl)-*N*-phenethyl-propionamide

3) 2-Propanoylamino-3-(2-propanoylamino-2-phenethylcarbamoyl-ethyldisulfanyl)-*N*-phenethyl-propionamide

4) 2-Hexanoylamino-3-(2-hexanoylamino-2-phenethylcarbamoyl-ethyldisulfanyl)-*N*-phenethyl-propionamide

5) 2-Phenacetylamino-3-(2-phenacetylamino-2-phenethylcarbamoyl-ethyldisulfanyl)-*N*-phenethyl-propionamide

6) 2-Cinnamoylamino-3-(2-cinnamoylamino-2-phenethylcarbamoyl-ethyldisulfanyl)-*N*-phenethyl-propionamide

7) 2-Benzoylamino-3-(2-benzoylamino-2-phenethylcarbamoyl-ethyldisulfanyl)-*N*-phenethyl-propionamide

8) 2-(4-Chlor-benzoyl)amino-3-(2-(4-chlor-benzoyl)amino-2-phenethylcarbamoyl-ethyldisulfanyl)-*N*-phenethyl-propionamide

9) 2-(4-Methyl-benzoyl)amino-3-(2-(4-methyl-benzoyl)amino-2-phenethylcarbamoyl-ethyldisulfanyl)-*N*-phenethyl-propionamide

10) 2-(4-Methoxy-benzoyl)amino-3-(2-(4-methoxy-benzoyl)amino-2-phenethylcarbamoyl-ethyldisulfanyl)-*N*-phenethyl-propionamide

11) 2-Methylsulfonylamino-3-(2-methylsulfonylamino-2-phenethylcarbamoyl-ethyldisulfanyl)-*N*-phenethyl-propionamide

12) 2-Ethylsulfonylamino-3-(2-ethylsulfonylamino-2-phenethylcarbamoyl-ethyldisulfanyl)-*N*-phenethyl-propionamide

13) 2-Benzylsulfonylamino-3-(2-benzylsulfonylamino-2-phenethylcarbamoyl-ethyldisulfanyl)-*N*-phenethyl-propionamide

14) 2-Benzenesulfonylamino-3-(2-benzenesulfonylamino-2-phenethylcarbamoyl-ethyldisulfanyl)-*N*-phenethyl-propionamide

15) 2-Toluolsulfonylamino-3-(2-toluolsulfonylamino-2-phenethylcarbamoyl-ethyldisulfanyl)-*N*-phenethyl-propionamide

16) 2-Formylamino-3-(2-formylamino-2-phenylmethylcarbamoyl-ethyldisulfanyl)-*N*-phenylmethyl-propionamide

17) 2-Formylamino-3-(2-formylamino-2-(2-phenylcyclopropyl)-carbamoyl-ethyldisulfanyl)-*N*-(2-phenylcyclopropyl)-propionamide

18) 2-Formylamino-3-(2-formylamino-2-morpholinoethylcarbamoyl-ethyldisulfanyl)-*N*-morpholinoethyl-propionamide

19) 2-Formylamino-3-(2-formylamino-2-cyclohexylethylcarbamoyl-ethyldisulfanyl)-*N*-cyclohexylethyl-propionamide

Experimental part

Example 1

2-(4-Chlor-benzoyl)amino-3-(2-(4-chlor-benzoyl)amino-2-phenethylcarbamoyl-ethyldisulfanyl)-N-phenethyl-propionamide

1) N,N'-Di-tert.butoxycarbonyl-L-cystin-bis-phenethylamide

N,N'-Di tert.butyloxycarbonyl-L-cystin (2.2 g) is dissolved in tetrahydrofurane (120 ml) and treated with N-hydroxybenzotriazole (1.35 g), O-(benzotriazole-1-yl)-N,N,N',N'-tetramethyluronium-tetrafluoroborat (4.27 g), di-isopropylethylamine (3.37 ml) and phenethylamine (1.38 ml). The mixture is stirred at room temperature for 4 hours and left over night without stirring. The reaction mixture was concentrated in vacuo. The residue was dissolved in dichloromethane and the organic phase washed two times with $NaHSO_4$-solution. A solid precipitated from the biphasic solvent mixture. The precipitate was filtered and the organic phase washed three times with $NaHCO_3$ solution and water. The filtrate was concentrated and the residue combined with the previously isolated precipitate to yield 3.18 g (98 %) of the title compound.
R_f silica gel = 0.66 (dichloromethane/methanol 95:5), m/e [M+H] = 647

1. L-Cystin-bis-phenethylamide

The product obtained by the above procedure (3.18 g) was dissolved in dichloromethane (30 ml) and trifluoro-acetic acid (8.16 ml). The mixture was kept at room temperature overnight , concentrated and neutralized with a solution of $NaHCO_3$ in water. The precipitate was filtered and washed with water to yield 1.22 g of the title compound.
R_f silica gel = 0.4 (dichloromethane/methanol 9:1)

3. 2-(4-Chlor-benzoyl)amino-3-(2-(4-chlor-benzoyl)amino-2-phenethylcarbamoyl-ethyldisulfanyl)-N-phenethyl-propionamide

4-Chlorobenzoic acid (156.5 mg) was dissolved in tetrahydrofurane (10 ml) and treated with 1-hydroxybenzotriazole (135 mg), O-(benzotriazole-1-yl)-N,N,N',N'-tetramethyluronium-tetrafluoroborat (389 mg), di- isopropylethylamine (342 µl) and L-cystin-bis-phenethylamide (223 mg) as a solution in 10 ml tetrahydrofurane. The reaction mixture was stirred for 24 hours. The precipitate was filtered washed with tetrahydrofurane and dried to yield 280 mg (77%) of the title compound.
TLC: Rf silica gel = 0.7 (dichloromethane/methanol 95:5)

Example 2

The compounds in the following table were synthesized using the procedure from exampled

Number	Chemical Name	TLC R_f value Silica gel
1	2-(Butanoyl)amino-3-(2-(butanoyl)amino-2-phenethylcarbamoyl-ethyldisulfanyl)-N-phenethyl-propionamide	0.5 dichlormethane/methanol 95:5
2	2-(4-Methylbenzoyl)amino-3-(4-methylbenzoyl)amino-2-phenethylcarbamoyl-ethyldisulfanyl)-N-phenethyl-propionamide	0.7 dichlormethane/methanol 95:5
3	2-((3-Benzoyl)-benzoyl)amino-3-(3-benzoyl)-benzoyl)amino-2-phenethylcarbamoyl-ethyldisulfanyl)-N-phenethyl-propionamide	0.7 dichlormethane/methanol 95:5
4	2-((Fluoren-1-yl-carbonyl)amino-3-(3-benzoyl)-benzoyl)amino-2-phenethylcarbamoyl-ethyldisulfanyl)- phenethyl-propionamide	0.75 dichlormethane/methanol 95:5
5	2-((Fluorenon-1-yl-carbonyl)amino-3-(3-benzoyl)-benzoyl)amino-2-phenethylcarbamoyl-ethyldisulfanyl)-N-phenethyl-propionamide	0.5 dichlormethane/methanol 95:5
6	2-(Pentanoyl)amino-3-(pentanoyl)amino-2-phenethylcarbamoyl-ethyldisulfanyl)-N-phenethyl-propionamide	0.65 dichlormethane/methanol 95:5
7	2-(4-Ethyl-biphenyl-1-yl-carbonyl)amino-3-(4-Ethyl-bi)amino-2-phenethylcarbamoyl-ethyldisulfanyl)-N-phenethyl-propionamide	0.65 dichlormethane/methanol 95:5
8	2-(3,4-Dichloro-benzoyl)amino-3-(3,4-dichloro-benzoyl)amino-2-phenethylcarbamoyl-ethyldisulfanyl)-N-phenethyl-propionamide	0.8 dichlormethane/methanol 95:5
9	2-(4-Phenoxy-benzoyl)amino-3-(4-phenoxy-benzoyl)amino-2-phenethylcarbamoyl-ethyldisulfanyl)-N-phenethyl-propionamide	0.8 dichlormethane/methanol 95:5
10	2-(4-Toluenesulfonyl)amino-3-(4-toluenesulfonyl)amino-2-phenethylcarbamoyl-ethyldisulfanyl)-N-phenethyl-propionamide	0.56 dichlormethane/methanol 95:5
11	2-(Propionyl)amino-3-(propionyl)amino-2-phenethylcarbamoyl-ethyldisulfanyl)-N-phenethyl-propionamide	0.4 dichlormethane/methanol 95:5
12	2-(4-Methylsulfonyl-benzoyl)amino-3-(4-methylsulfonyl-benzoyl)amino-2-phenethylcarbamoyl-ethyldisulfanyl)-N-phenethyl-propionamide	0.31 dichlormethane/methanol 95:5

13	2-(4-Chloro-phenylacetyl)amino-3-(4-Chloro-phenyl-acetyl)amino-2-phenethylcarbamoyl-ethyldisulfanyl)-N-phenethyl-propionamide	0.8 dichlormethane/methanol 90:10
14	2-(4-Methyl-cinnamoyl)amino-3-(4-methyl-cinnamoyl)amino-2-phenethylcarbamoyl-ethyldisulfanyl)-N-phenethyl-propionamide	0.3 dichlormethane/methanol 95:5
15	2-(4-Methyl-phenylacetyl)amino-3-(4-methyl-phenyl-acetyl)amino-2-phenethylcarbamoyl-ethyldisulfanyl)-N-phenethyl-propionamide	0.37 dichlormethane/methanol 95:5
16	2-(4-Methoxy-benzoyl)amino-3-(4-methoxy-benzoyl)amino-2-phenethylcarbamoyl-ethyldisulfanyl)-N-phenethyl-propionamide	0.65 dichlormethane/methanol 95:5
17	2-(4-Methoxy-cinnamoyl)amino-3-(4-methoxy-cinnamoyl)-amino-2-phenethylcarbamoyl-ethyldisulfanyl)-N-phenethyl-propionamide	0.67 dichlormethane/methanol 95:5
18	2-(4-Chloro-cinnamoyl)amino-3-(4-chloro-cinnamoyl)-amino-2-phenethylcarbamoyl-ethyldisulfanyl)-N-phenethyl-propionamide	0.58 dichlormethane/methanol 95:5
19	2-(Acetyl)amino-3-(acetyl)-amino-2-phenethylcarbamoyl-ethyldisulfanyl)-N-phenethyl-propionamide	0.25 dichlormethane/methanol 95:5

Example 3

2-(Benzyloxycarbonyl)amino-3-(2-(benzyloxycarbonyl)amino-2-hexylcarbamoyl-ethyldisulfanyl)-N-hexyl-propionamide

Di-benzyloxycarbonyl-L-cystine (508 mg) was dissolved in tetrahydrofurane (25 ml) and treated with 1-hydroxybenzotriazole (270 mg), O-(Benzotriazole-1-yl)-N,N,N',N'-tetramethyluronium-tetrafluoroborat (777 mg) and di-isopropylethylamine (0.68 ml). The mixture was stirred for 10 min and n-hexylamine (0.29 ml) was added. After stirring overnight the reaction mixture was concentrated . The residue was dissolved in ethyl acetate, washed two times with $NaHSO_4$ solution , $NaHCO_3$ solution and water. The organic phase was dried and concentrated. The residue was triturated with isohexane to yield 550 mg (77%) of the title compound.
R_f (silica gel) = 0.3 (dichloromethane/methanol 97:3)

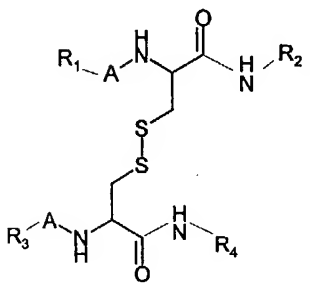
Example 4

The compounds in the following table were synthesized using the procedure of example 4

Number	Chemical name	TLC R_f value Silica gel
1	2-(Benzyloxy-carbonyl)amino-3-(benzyloyxcarbonyl)-amino-2-4-fluoro-phenethyl-carbamoyl-ethyldisulfanyl)-N-4-fluoro-phenethyl-propionamide	0.72 dichloromethane/methanol 97:3
2	2-(Benzyloxy-carbonyl)amino-3-(benzyloyxcarbonyl)-amino-2-3,4-dimethoxy-phenethyl carbamoyl-ethyldisulfanyl)-N-3,4-dimethoxy-phenethyl-propionamide	0.3 dichloromethane/methanol 97:3
3	2-(Benzyloxy-carbonyl)amino-3-(benzyloyxcarbonyl)-amino-2- morpholino-propyl carbamoyl-ethyldisulfanyl)-N-morpholino-propyl-propionamide	0.4 dichloromethane/methanol 95:5
4	2-(Benzyloxy-carbonyl)amino-3-(benzyloyxcarbonyl)-amino-2-4-imidazolyl-ethyl carbamoyl-ethyldisulfanyl)-N-4-imidazolyl-ethyl-propionamide	0.6 dichloromethane/methanol 80:20
5	2-(Benzyloxy-carbonyl)amino-3-(benzyloyxcarbonyl)-amino-2-4-chloro-phenethyl carbamoyl-ethyldisulfanyl)-N-(4-chloro-phenethyl)-propionamide	0.77 dichloromethane/methanol 97:3
6	2-(Benzyloxy-carbonyl)amino-3-(benzyloyxcarbonyl)-amino-2-(3-indolyl-ethyl)-carbamoyl-ethyldisulfanyl)-N-(3-indolyl-ethyl)-propionamide	0.6 dichloromethane/methanol/ammonia conc. 16:4:0.1
7	2-(Benzyloxy-carbonyl)amino-3-(benzyloyxcarbonyl)-amino-2-phenethyl-carbamoyl-ethyldisulfanyl)-N-phenethyl-propionamide	0.45 dichloromethane/methanol 98:2

Patent Claims

1. A pharmaceutically composition containing non peptidic cystine derivatives of the general formula I



(I)

wherein

R_1 and R_3 may be the same or different and are selected from hydrogen, an aromatic or non-aromatic carbocyclic or heterocyclic ring or a linear or branched saturated or unsaturated alkyl group of 1 to 15 carbon atoms which can be interrupted by a hetero atom and which can be substituted by an aromatic or non-aromatic carbocyclic or heterocyclic ring.

R_2 and R_4 may be the same or different and are selected from hydrogen, a linear or branched, saturated or unsaturated alkyl group of 1 to 15 carbon atoms which can be interrupted by a hetero atom and which can be substituted by an aromatic or non-aromatic carbocyclic or heterocyclic ring and

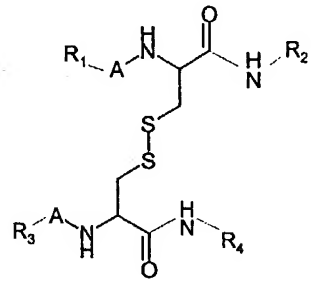
A is a valency bond or a-CO-, -SO_2-, -NHCO-, -NHCS- or –O-CO-group

their pharmacologically acceptable salts and optically active forms thereof and pharmaceutically acceptable carriers.

2. Use of a compound according to formula I of claim 1 for the preparation of a medicament containing a compound of formula I as active ingredient for treatment of diseases selected from tumor growth and metastasis, inflammatory diseases like osteo- and rheumatoid arthritis, osteoporosis, multiple sclerosis, periodonititis, restenosis, diseases caused by bacteria such as meningitis, sun-induced skin aging and Alzheimers disease.

3. Use of compound according to formula I of claim 1 for the preparation of a medicament containing a compound of formula I as active ingredient for the treatment of MMP-related diseases such as tumor growth and metastasis, inflammatory diseases like osteo- and rheumatoid arthritis, osteoporosis, multiple sclerosis, periodontitis, restenosis, diseases caused by bacteria such as meningitis, sun-induced skin aging and Alzheimers disease.

4. New compounds of formula I



(I)

wherein

R_1 and R_3 may be the same or different and are selected from hydrogen, an aromatic or non-aromatic carbocyclic or heterocyclic ring or a linear or branched saturated or unsaturated alkyl group of 1 to 15 carbon atoms which can be interrupted by a hetero atom and which can be substituted by an aromatic or non-aromatic carbocyclic or heterocyclic ring.

R_2 and R_4 may be the same or different and are selected from hydrogen, a linear or branched, saturated or unsaturated alkyl group of 1 to 15 carbon atoms which can be interrupted by a hetero atom and which can be substituted by an aromatic or non-aromatic carbocyclic or heterocyclic ring and

A is a valency bond or a-CO-, -SO_2-, -NHCO-, -NHCS- or –O-CO-group

with the proviso that if R_2 and R_4 are benzyl, R_1-A and R_3-A cannot be formyl, C_1-C_{10} alkylcarbonyl, benzoyl, toluenesulfonyl or benzyloxycarbonyl, and

if R_1-A and R_3-A are benzyloxycarbonyl, R_2 and R_4 cannot be pyridylmethyl, phenylethyl, 4-hydroxyphenylethyl, 4-chlorophenylethyl, phenylpropyl or indolylethyl

their pharmacologically acceptable salts and optically active forms thereof.